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(19)

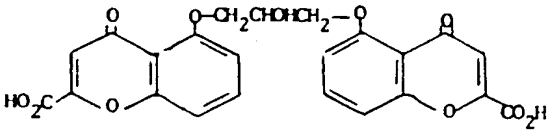
(54) TABLETS CONTAINING 1,3-BIS(2-CARBOXYCHROMON-5-YLOXY)-2-HYDROXYPROPANE

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London W1X 0AH do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention concerns pharmaceutical compositions.

The compound disodium cromoglycate (the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane) has been known for some time as a treatment for asthma by inhalation of a powder containing it. It has recently been demonstrated that this compound is also useful in the treatment of various conditions of the gastro-intestinal tract in which allergic or immune reactions play a contributory part. However, when administered orally to a patient in any of the conventional formulations for other drugs it is found that the acidic conditions in various regions of the gastro-intestinal tract tend to convert the disodium salt to the acid itself, which is insoluble. As a result, a thick gum-like surface coating, impervious to water, is formed over the particles, granules or agglomerates of the salt, thereby preventing them from dissolving or dispersing and thus effectively reducing their availability. We have now found a formulation which avoids or at least mitigates this problem.

Accordingly, in one aspect, this invention provides a pharmaceutical composition in the form of a tablet disintegrable in the presence of further water and comprising from 5 to 80% by weight of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane of the formula:



or a pharmaceutically-acceptable salt thereof, in association with from 20 to 95% by weight of a mixture of an alkali-metal or alkaline earth metal carbonate or bicarbonate and citric acid, the tablet having an equilibrated relative humidity of less than 25%.

Pharmaceutically-acceptable salts of the bis-chromone include the alkali-metal salts, for example the di-sodium and di-potassium salts, and the alkaline earth metal salts, for example the calcium and magnesium salts. The sodium salt is especially preferred.

The tablet preferably contains from 30 to 75%, especially from 35 to 65% by weight of the bis-chromone.

The carbonate or bicarbonate may, for example, be sodium or potassium carbonate or bicarbonate, sodium bicarbonate being especially preferred, and is desirably present in an amount of from 25 to 50%, especially from 25 to 35%, by weight of the tablet.

The citric acid is desirably present in an amount of from 15 to 55% by weight of the tablet.

The equilibrated relative humidity may for example be determined by a SINA equi-hygroscope eZFBA (from Nova-Sina Limited, Zurich). It is preferably less than 20%. Where water is employed as the granulating solvent the equilibrated relative humidity is

preferably greater than 15%, although it may be lower if non-aqueous granulating solvents, e.g. isopropyl alcohol, are employed. In such a case it may desirably be from 9 to 20%.

Although the tablet may be composed entirely of the bis-chromone, the carbonate or bicarbonate and the acid, other diluents, carriers, binders or adjuvants may be incorporated into the tablet if desired. As an example, it is usually preferred to incorporate up to 2% by weight, for example 0.25-1% by weight, of a pharmaceutically-acceptable lubricating agent, for example magnesium lauryl sulphate or magnesium stearate, in order to facilitate manufacture of the tablets.

The molar ratio of the carbonate or bicarbonate to the acid is preferably such as to allow substantially complete reaction between them, i.e. they are preferably present in stoichiometric amounts. Preferred weight ratios of sodium or potassium bicarbonate to citric acid are thus preferably from 1.2:1 to 1.7:1.

The tablets are disintegrable in the presence of further water, e.g. in the stomach, to give either a solution of the bis-chromone if water-soluble or a finely-dispersed suspension of the bis-chromone if water-insoluble.

The tablets of the invention may be produced by conventional tabletting techniques except that granulation, if effected in an aqueous solvent, must take place before admixture of the carbonate or bicarbonate and the citric acid.

The tablets of the present invention are of use in the treatment in man of conditions of the stomach or gastro-intestinal tract after the stomach, in which conditions, allergy or immune reactions play a contributory part. Conditions which may be treated include Crohn's disease (a condition of the small, and sometimes also of the large, intestine), atrophic gastritis (a condition of the stomach), ulcerative colitis (a condition of the rectum), proctitis (a condition of the rectum and lower large intestine), coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum), gastro-intestinal allergy (e.g. gluten or other food allergy), and irritable bowel syndrome.

The dosage to be administered will of course depend upon the condition to be treated and its severity. However, in general, a total daily dosage of from 100 to 4,000 mg of the bis-chromone, and more preferably from 400 to 2,000 mg thereof, administered in smaller doses 2 to 4 times per day is found to be satisfactory. A dosage unit may conveniently contain from 50 to 500 mg of the bis-chromone.

Preferably administration takes place a short time, for example about 30 minutes, before the patient takes food.

The following Examples are now given, though only by way of illustration.

Example 1

The following ingredients were formulated into tablets of the invention by the method described hereinafter:

	mg per tablet
1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane, disodium salt	200
Sodium bicarbonate BP	120
Citric acid (granular) BP	91.2
Magnesium stearate	1.03
Water	Approx 12
	424.23

An excess of the disodium salt was sieved through a 36 mesh screen and its moisture content was determined. The appropriate quantity to give 200 mg/tablet was then calculated and mixed with the appropriate quantity of granular sodium bicarbonate. Water was then sprayed into the mixer to give a moisture content of 20% by weight. The temperature was maintained at below 35°C, and the wet mass was passed through an 8 mesh screen on an oscillating granulator. The granules were then part-dried in a fluid bed drier at 100°C, passed through a 20 mesh screen, and further dried to a moisture content below 20% equilibrated relative humidity, and were then blended with the citric acid and the magnesium stearate in a drum roller. The mix was then compressed to give tablets, which

were stored at less than 30% relative humidity at 20°C and strip-packed individually.

Example 2

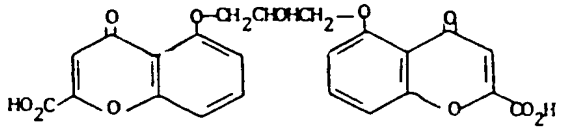
The following ingredients were formulated into tablets of the invention as follows:

	mg/tablet
1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane, disodium salt	200
Sodium bicarbonate BP	120
Citric Acid BP	91.2
Magnesium Lauryl Sulphate	2.06
Water	Approx 8
	421.26

The chromone salt is dried to a moisture content of less than 5% by weight, and the other ingredients are dried to less than 0.5% by weight. All the ingredients except the magnesium lauryl sulphate were dry mixed in a suitable blender and were granulated with isopropyl alcohol (moisture content less than 0.25%) approximately 500 ml of the alcohol being employed per kg of the powder mixture. The mass was then passed through an 8 mesh screen on a rotary granulator, dried on a fluid bed drier, and passed through a 20 mesh screen. The magnesium lauryl sulphate was then blended in and the mixture was compressed into tablets (> 8 kp Schleuniger). Throughout, all operations were effected in flame-proof equipment in an atmosphere of less than 30% relative humidity at 20°C or equivalent.

WHAT WE CLAIM IS:-

1. A pharmaceutical composition in the form of a tablet disintegrable in the presence of water and comprising from 5 to 80% by weight of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane of the formula:



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or a pharmaceutically-acceptable salt thereof, in association with from 20 to 95% by weight of a mixture of an alkali-metal or alkaline earth metal carbonate or bicarbonate and citric acid, the tablet having an equilibrated relative humidity of less than 25%.

2. A composition according to claim 1 wherein the bis-chromone is employed in the form of the disodium salt thereof.

3. A composition according to claim 1 or claim 2 wherein the tablet contains from 30 to 75% by weight of the bis-chromone.

4. A composition according to claim 3 wherein the table contains from 35 to 65% by weight of the bis-chromone.

5. A composition according to any of claims 1 to 4 wherein the carbonate or bicarbonate is sodium or potassium carbonate or bicarbonate.

6. A composition according to any of claims 1 to 5 wherein the carbonate or bicarbonate is present in an amount of from 25 to 50% by weight.

7. A composition according to claim 6, wherein the carbonate or bicarbonate is present in an amount of from 25 to 35% by weight.

8. A composition according to any of claims 1 to 7, wherein the citric acid is present in an amount of from 15 to 55% by weight of the tablet.

9. A composition according to any of claims 1 to 7 the equilibrated relative humidity of which is from 9 to 20%.

10. A composition according to claim 9 the equilibrated relative humidity of which is greater than 15%.

11. A composition according to any of claims 1 to 10, wherein the carbonate or bicarbonate and the citric acid are present in substantially stoichiometric amounts.

12. A composition according to any of claims 1 to 11 in unit dosage form containing from 50 to 500 mg of the bis-chromone.

13. A composition according to any of claims 1 to 12 and substantially as described herein with reference to the Examples.

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